

Hypoderma spp. investigation of dynamic Thiol disulfide balance in infested cattle

Investigación del equilibrio dinámico Tíol-Disulfuro en ganado infestado con Hypoderma spp

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ABSTRACT

Hipodermiasis in cattle is a parasitic disease caused by *Hypoderma bovis* and *Hypoderma lineatum* type fly larvae. The disease, which mostly affects young cattle, causes economic losses such as developmental delay, decrease in meat and milk yield, and inability to use the back skin as a result of being punctured by the larvae. This study aimed to determine serum total thiol, native thiol, disulfide, interleukin-1, IL-6, and tumor necrosis factor- α levels in Hypoderma-infested cattle. In the study, 15 Hypoderma infested cattle diagnosed by clinical examination and 10 healthy cattle for control purposes were used. Serum total thiol, native thiol and disulphide levels of the sick animals were determined as $406.84 \pm 8.33 \mu\text{mol/L}$, $297.62 \pm 5.24 \mu\text{mol/L}$, $54.61 \pm 4.83 \mu\text{mol/L}$, respectively. interleukin-1, interleukin-6 and tumor necrosis factor- α were detected as $41.98 \pm 4.37 \text{ pg/mL}$, $94.11 \pm 8.49 \text{ pg/mL}$, $82.29 \pm 9.12 \text{ pg/mL}$ in infested animals. Total thiol, native thiol and disulfide values of infested animals were determined to be lower than the healthy control group, and interleukin-1, interleukin-6, and tumor necrosis factor- α were higher than those of healthy animals. As a result, interleukin-1, interleukin-6, and tumor necrosis factor- α values were determined to be high, and total thiol and native thiol levels were low in cattle with hipodermiasis.

Key words: Hipodermiasis; interleukin-1; interleukin-6; native thiol; bovine; tumor necrosis factor- α ; total thiol.

RESUMEN

Hipodermiasis en el ganado es una enfermedad parasitaria causada por larvas de moscas de los tipos *Hypoderma bovis* e *Hypoderma lineatum*. La enfermedad, que afecta principalmente al ganado joven, provoca pérdidas económicas como retraso en el desarrollo, disminución en la producción de carne y leche, y la incapacidad de usar la piel del lomo debido a las perforaciones causadas por las larvas. El objetivo de este estudio fue determinar los niveles séricos de tíol total, tíol nativo, disulfuro, interleucina-1, IL-6 y factor de necrosis tumoral- α en ganado infestado con Hypoderma. En el estudio se utilizaron 15 bovinos infestados con Hypoderma, diagnosticados mediante examen clínico, y 10 bovinos sanos como grupo control. Los niveles séricos de tíol total, tíol nativo y disulfuro de los animales enfermos se determinaron como $406.84 \pm 8.33 \mu\text{mol/L}$, $297.62 \pm 5.24 \mu\text{mol/L}$, $54.61 \pm 4.83 \mu\text{mol/L}$ respectivamente. interleucina-1, interleucina-6 y factor de necrosis tumoral- α se detectaron como $41.98 \pm 4.37 \text{ pg/mL}$, $94.11 \pm 8.49 \text{ pg/mL}$, $82.29 \pm 9.12 \text{ pg/mL}$ en los animales infestados. Los valores de tíol total, tíol nativo y disulfuro de los animales infestados se determinaron como más bajos que los del grupo control sano, y los de interleucina-1, interleucina-6 y factor de necrosis tumoral- α fueron más altos que los de los animales sanos. Como resultado, los valores de interleucina-1, interleucina-6 y factor de necrosis tumoral- α se determinaron como altos, y los niveles de tíol total y tíol nativo como bajos en el ganado con hipodermiasis.

Palabras clave: Hipodermiasis; interleucina-1; interleucina-6; tíol nativo; bovino; factor de necrosis tumoral- α ; tíol total.

INTRODUCTION

Hypodermosis is a parasitic disease caused by the larval stage of flies belonging to the *Hypoderma genus* (Diptera, Oestridae) in cattle (*Bos taurus*) and progresses with myiasis. Since *Hypoderma bovis* and *Hypoderma lineatum* are characterized by the presence of limited and distinct subcutaneous swellings made by the larvae on the back and waist region of cattle, they can be easily detected by palpation (clinical parasitological examination) on the backs of animals in spring and summer [1].

In cattle affected by the disease, significant economic losses occur due to a significant decrease in meat and milk yield, growth retardation and irreversible damage to the skin. In addition, it is extremely difficult to evaluate the possible stress caused by hypodermiasis and the immunosuppression effect that may result from it, as well as the economic losses that may be caused by secondary infections caused by bacteria, viruses, etc [2].

Development of hipodermiasis; First, the first stage larvae (L1) of adult flies penetrate the skin by depositing them on the hind legs, hind ankles and lower abdominal area of cattle. In this region, they cross the skin with L1 enzymatic secretions. L1, which crosses the skin, passes through the host connective tissue. They then move through the subcutaneous tissues and migrate under the back skin. It may take 8-10 months for the larva to enter the body, migrate and leave [2].

It has been reported that the migration of the larvae and, most recently, myiasis, which is characterized by subcutaneous boils on the back and waist of the animals during the summer months, cause inflammation and stress in the host [2].

It has been reported that parasitic factors cause inflammation. In chronic inflammation, proinflammatory cytokines are released from macrophages in the vascular wall. A significant portion of these cytokines are interleukins [3]. Of these, interleukin (IL)-1, IL-6 and tumor necrosis factor- α (TNF- α) activate immune system cells [4, 5]. TNF- α causes the secretion of cytokines and chemokines and the migration and proliferation of lymphocytes to the inflammation site [6]. IL-1, in conjunction with TNF- α , is a pro-inflammatory cytokine that can affect almost every cell type [7]. IL-6 is both a pro- and anti-inflammatory cytokine that has been associated with disease states and is produced by various cell types in situations of infection and trauma [8].

It has been determined that as a result of inflammation resulting from increased skin-subcutaneous-connective tissue damage in cattle with hipodermiasis, endothelial damage, dysfunction and oxidative stress occur due to this process [9, 10, 11]. It is effective in tissue damage through mechanisms such as lipid peroxidation and protein oxidation. An important reason for decreased antioxidant levels in the body is increases in free radicals or reactive oxygen species. These increases lead to imbalance and as a result oxidative stress occurs. It has been demonstrated by frequent studies in recent years that oxidative stress plays a role in the pathological process of many diseases in Veterinary Medicine [11].

At the cellular level, proteins function not only as structural building blocks but also as sensitive molecular machines that respond to environmental changes. The dynamic functions and structural integrity of proteins depend on the delicate redox balance provided by the sulfur-containing amino acids cysteine

and methionine. The sulfhydryl (-SH) groups of these amino acids act as molecular sensors that detect oxidative changes in the cellular microenvironment [12, 13].

Under oxidative stress conditions, an increase in reactive oxygen species such as hydrogen peroxide targets these sensitive sensors, initiating the oxidation process. In the initial stage of the reaction, the -SH groups convert into sulfonic acid, an unstable and highly reactive form. As long as oxidative stress persists, the conversion of these structures into disulfide bonds acts as a molecular shield that protects the protein from permanent damage and maintains its functional integrity. The thiol-disulfide homeostasis maintained by the reconversion of these disulfide bonds back into thiol groups via cellular reductive mechanisms serves not only as an early indicator of protein oxidation but also as a critical adaptive strategy for cellular survival [12, 14].

This dynamic balance serves as a vital control mechanism in fundamental processes regulating cellular homeostasis, such as apoptosis, regulation of enzymatic activity, antioxidant defense, and detoxification [13, 14, 15, 16]. Changes in thiols and pro-inflammatory cytokines observed in parasitic infections such as hypodermosis are a systemic reflection of these complex oxidative and inflammatory processes. Although the role of this mechanism in pathophysiological processes has been elucidated by extensive literature in human medicine, research on the clinical and pathophysiological significance of this biochemical balance in the field of veterinary medicine remains limited.

This study aims to evaluate the systemic response that develops secondary to tissue damage caused by parasite larvae during the seasonal phase of hypodermosis, focusing on changes in the pro-inflammatory cytokine profile (TNF- α , IL-1, IL-6) and in thiol-disulfide homeostasis, a sensitive indicator of protein oxidation.

MATERIALS AND METHODS

Ethical Statement

The protocol for this research was formally sanctioned by the Local Ethics Committee for Animal Experiments at Kafkas University (Reference: KAU-HADYEK/2021-080).

Animal Selection

The presence of hypodermiasis in cattle in Türkiye has been documented in various studies [17, 18]. Since it has been reported that acquired immunity develops in cattle exposed to *Hypoderma* spp. twice or more, this study was specifically conducted on animals naturally exposed to the disease for the first time [19, 20, 21, 22]. Furthermore, it has been reported that the number of warbles significantly affects the biochemical parameters obtained from such studies [20]. Based on this literature, animals presenting with 4 to 10 warbles on their dorsal and lumbar regions were preferred for the study.

Animal Material

The study involved a total of 25 cattle, aged 18–24 months. The experimental group consisted of 15 animals naturally infested with 8–10 *Hypoderma* spp. larvae (warbles), while 10 healthy cattle served as the control group. The sample size for the control group (n = 10) was determined following the

ethical principle of 'Reduction' in animal research. Given the high homogeneity and low standard deviation of biochemical parameters typically observed in healthy animals, this sample size was deemed sufficient to establish a statistically reliable baseline. In contrast, 15 animals were included in the infested group to better account for potential variations in individual clinical and biochemical responses. Statistical analysis confirmed that the difference in group sizes did not compromise the power or the validity of the results.

To obtain serum samples, blood was drawn from the jugular vein and subjected to centrifugation at 3000 rpm for a duration of 10 minutes (Zenith Lab LC-04B, China). Separated sera were then transferred to storage at -80 °C (Esco Lexicon® UUS-48OB-1-5D, Singapore) to maintain stability until biochemical profiling. The age, gender, care and feeding conditions of the animals included in the study were the same.

Biochemical analysis

Serum thiol concentrations were measured using the colorimetric spectrophotometric technique described by Erel and Neselioglu [13] with an Agilent Technologies Cary 60 UV-Vis system (USA). Additionally, pro-inflammatory cytokines (TNF- α , IL-1, and IL-6) were measured using commercial ELISA kits (BT Lab, China) following the manufacturer's instructions.

Statistical analysis

Data were processed using SPSS 20.0. Normal distribution was confirmed, and an independent t-test was utilized for comparisons. Results are presented as mean \pm standard deviation, with significance set at $P < 0.05$.

RESULTS AND DISCUSSION

In the measurements made; While a general decrease was detected in the values for thiol/disulfide balance, statistically significant decreases were determined only in total thiol and native thiol values. The values obtained from the infested hypodermic group and the control group are given in TABLE I.

Parameters	Infested group	Control group	P
TT ($\mu\text{mol/L}$)	406.84 \pm 8.33	459.25 \pm 16.20	$P < 0.01$
NT ($\mu\text{mol/L}$)	297.62 \pm 5.24	327.68 \pm 11.72	$P < 0.05$
Ds ($\mu\text{mol/L}$)	54.61 \pm 4.83	65.78 \pm 6.89	NS
Ds/NT (%)	18.66 \pm 1.86	20.58 \pm 2.36	NS
Ds/TT (%)	13.24 \pm 0.93	14.04 \pm 1.18	NS
NT/TT (%)	73.52 \pm 1.86	71.93 \pm 2.35	NS

NT - native thiol, TT - total thiol, Ds - disulfide, Data are presented as the mean \pm SD, NS: no significativo

In the study, TNF- α , IL-1 and IL-6 parameters obtained from the *Hypoderma* group were found to be statistically significantly higher than the control group. The values obtained from the hypodermic group and the control group are given in TABLE II.

Parameters	Control group	Infested	P
TNF- α (pg/mL)	82.29 \pm 9.12	177.78 \pm 9.62	$P < 0.001$
IL-1 (pg/mL)	41.98 \pm 4.37	149.80 \pm 8.88	$P < 0.001$
IL-6 (pg/mL)	94.11 \pm 8.49	129.69 \pm 5.02	$P < 0.01$

TNF- α - tumor necrosis factor-alpha, IL-1 - interleukin-1, IL-6 - interleukin-6.

These study demonstrates that a significant shift in the thiol-disulfide balance leads to systemic oxidative stress characterized by increased protein oxidation which drives the pathological process of hypodermosis. These findings are consistent with the existing literature indicating that physiological abnormalities trigger free radical production [11, 23]. Furthermore, the critical role of thiol-disulfide homeostasis in apoptosis, antioxidant defense, and intracellular signaling [24, 25, 26, 27] underscores the systemic impact of the infection. These results demonstrate that this balance is not only affected in human diseases [16, 10, 28], but also functions as a sensitive diagnostic marker for oxidative damage in cattle with hypodermosis, providing further evidence of the clinical importance of thiol groups in pathological conditions.

In Veterinary Medicine; in calves dehorned with hot cautery [19], in dogs (*Canis lupus familiaris*) with distemper [29], in sheep (*Ovis aries*) with gastrointestinal nematodes [30], in sheep with toxoplasmosis [31]. Studies have reported that native thiol (NT) and total thiol (TT) levels are low. In the same studies, disulphide (Ds), disulphide/native thiol (Ds/NT), disulphide/total thiol (Ds/TT) were reported to be high. Among the reported results, NT, TT and Ds levels obtained from sheep infested with sarcoptic mange, which has high dermatological effects, decreased and there was no difference in Ds/NT, Ds/TT and native thiol / total thiol (NT/TT) ratios [32].

Unlike these studies, Deveci and Erdal [33] found an increase in NT and TT levels in cattle foot diseases. Studies conducted in recent years show an increase in reactive oxygen species as well as a decrease in plasma thiol concentration as an indicator of oxidative stress [31, 34, 35]. In the presented study, it was determined that NT and TT values of the infested group were low. It is thought that the decrease in TT and NT levels obtained in this study can be explained by tissue damage caused by subcutaneous factors, strong oxidative stress caused by inflammation, and the severity of thiol oxidation affected by oxidative stress, as noted in the studies of other researchers. The formation of subepidermal tunnels during the developmental period of hypoderma larvae causes myiasis subcutaneous inflammation accompanied by raised and serpentine lesions until they leave the animal. As a defense reaction against parasites that cause tissue damage, pro-inflammatory cytokines such as TNF- α , IL-1 and IL-6 are released from activated leukocytes in the region and from macrophages in the vessel wall as a result of chronic inflammation. IL-1 plays an important role in the initiation of inflammation in the pathogenesis of skin diseases. It has been reported that levels of IL-1, its derivatives IL-1 α and IL-1 β , increase in humans infested with scabies mites [36].

In a study conducted in cattle with anaplasma, it was determined that there was an increase in IL-6 level. It is stated

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that this increase is caused by the stimulation of macrophages by factors and the increase in the synthesis of pro-inflammatory cytokines [37]. In other study conducted in cattle with trichophytosis, it was reported that TNF- α , IL-1 and IL-6 values were statistically significantly higher than the control group [38].

In this study, IL-1 and IL-6 were found to be statistically higher and more significant compared to the control group, which is thought to be due to the inflammation that occurs as a result of the migration of the larva and the perforation in the skin.

Tumor necrosis factor- α is one of the first immune mediators released from activated T cells and macrophages as a pro-inflammatory cytokine [5, 39]. TNF- α is the predominant cytokine in bovine serum. In a study where TNF- α was used to monitor the prognosis of cattle with mastitis, it was reported that the serum TNF- α level of sick animals was significantly increased [40].

High TNF- α levels in the skin and serum of hypoderma-infested cattle have been reported in studies [41]. It has been reported that there is an increase in cytokines after boils appear on the back in cattle infested with *H. lineatum* [42]. In this study, 4-8 larvae were seen on the dorsal areas of young hypodermic cattle and healthy samples of the same age were taken as control group.

The average levels of TNF- α measured in the blood serum of the patients were determined as 177.78 pg/mL and 82.29 pg/mL, respectively. The average TNF- α in the control group was determined as 84 pg/mL, according to Ercan *et al.* [43] are similar to the levels they determined in healthy cattle. Similar to the findings determined in this study, the fact that TNF- α level was measured higher in the hypodermic group compared to the control group shows that TNF- α can be considered a biomarker indicating inflammation in cattle [22, 44].

Tumor necrosis factor- α was found to be higher compared to the control group and this difference was found to be statistically significant. It was determined that the results obtained in the study were compatible with the results of previous studies conducted by other researchers.

CONCLUSIONS AND IMPLICATIONS

This study determined the levels of TT, NT, Ds (and their interactions), TNF- α , and IL-1 to IL-6 in animals with hypodermiasis. It was observed that the thiol-disulfide balance shifted towards disulfide in hypodermiasis-affected animals, and systemic oxidative damage occurred along with protein oxidation. Changes in TT, NT, and Ds parameters, and increases in TNF- α and IL-1 to IL-6 levels, indicated that myiasis-induced tissue damage both disrupts the redox system and creates a severe inflammatory response.

Furthermore, protein oxidation was observed in hypodermiasis. Determining the thiol-disulfide balance, an indicator of protein oxidation, could serve as a prognostic biomarker in patients with hypodermiasis. Thiol/disulfide balance can be used to determine oxidative stress and antioxidant status in proliferative and inflammatory diseases.

Conflicting interest

The authors have no conflicts of interest to declare.

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